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(54) Title: A SKIN LIGHTENING COMPOSITION CONTAINING AN ASCORBIC ACID COMPOUND

(57) Abstract

Disclosed is a composition comprising: (a) an ascorbic acid compound; (b) a charged, reflective particulate material a preferred embodiment of which is coated Titanium dioxide; (c) a structuring compound whose preferred embodiment is a combination of a surfactant and a fatty alcohol; and a cosmetically-acceptable carrier. Preferred use of such composition is a skin whitening composition. Herein, ascorbic acid compound means ascorbic acid or derivatives thereof which have formula: (II) wherein R2 and R3 are independently selected from hydrogen and linear or branched alkyl of 1 to about 8 carbons; M1 is a metal; and x is an integer of from 1 to about 3. More preferably, R² and R³ are independently selected from hydrogen and linear or branched alkyl of 1 to about 3 carbons; M¹ is sodium, potassium, magnesium, or calcium.

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A SKIN LIGHTENING COMPOSITION CONTAINING AN ASCORBIC ACID COMPOUND

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FIELD

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The present invention relates to a topical composition. In particular, it relates to a topical skin lightening composition.

BACKGROUND

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Consumers frequently use cosmetic products to care for their skin as well as to improve the health and/or physical appearance of their skin. Rough and/or broken skin and hyperpigmentations (such as age spots, freckles, and brown patches associated with sunlight exposure, skin aging or environmental damage to the human skin) are areas consumers typically seek to treat. Skin lightening is of particular interest in certain Asian populations.

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Irradiation of ultra-violet (UV) rays tends to cause sun-burning, resulting in skin darkening and/or hyperpigmentation. It is generally known that conditions which result in defective or missing tyrosinase, an enzyme involved in the formation of melanin, lead to hyperpigmentation, e.g. albinism. The irradiation of UV rays as a consequence of exposure to sunlight promotes a melanin complex formation in melanocytes located in the basal layer of the epidermis. Melanin is subsequently released from the dendrites of the melanocytes, then diffused to keratinocytes. resulting in hyperpigmentation of the skin. Such hyperpigmentation may take the form of spots, freckles, blotches, unwelcome general darkening and/or unevenness of the basal skin.

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A wide variety of compounds and/or ingredients, e.g., ascorbic acid and derivatives thereof, kojic acid and derivatives thereof, hydroquinone, arbutine, and a variety of extracts such as glycyrrhiza, are known and are commonly-available for skin-lightening use. In recent years, hi-tech synthetic ingredients

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useful for skin-lightning are also available in a wide variety and array of product forms.

L-ascorbic acids (e.g., Vitamin C) are useful ingredients as skin-lightening and/or evenness agents as well as a reductant, UV-absorbent and melaninformation inhibitor in cosmetics. However, it is also known that L-ascorbic acid tends to be unstable in formulation, resulting in imparting a (undesirable) yellowish color to the composition which may eventually become brownish. This may lead deterioration of a product value.

Certain combinations have been designed to stabilize compositions containing ascorbic acids. Japanese Laid-open (Kokai) H1-213212, Imamura et al., issued August 28, 1989, discloses stable cosmetic compositions containing ascorbic acid derivatives and gluconic acids. Japanese Laid-open H1-305009, Yamada et al., issued December 8, 1989, discloses stable cosmetic compositions containing ascorbic acid derivatives and cyclodextrin. Japanese Laid-open H3-63208, Sato, issued March 19, 1991, discloses compositions containing ascorbic acid and phenoxyethanol. Such combinations tend to provide acceptable stability of the compositions, but the product appearance change to yellow or brown is still observed, especially in storage. It would therefore be desirable to stabilize compositions containing ascorbic acid, particularly while at the same time increasing the levels of ascorbic acid present in formulation.

Based on the foregoing, there is a need for a stable skin lightening composition having increased levels of ascorbic acid compound as well as sustained pleasant product aesthetics. None of the existing art provides all of the advantages and benefits of the present invention.

SUMMARY

The present invention is directed to a composition comprising:

- (a) an ascorbic acid compound;
- (b) a charged, reflective particulate material;
- (c) a structuring compound; and
- (d) a cosmetically-acceptable carrier.

These and other features, aspects, and advantages of the present invention will become better understood from a reading of the following description, and appended claims.

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DETAILED DESCRIPTION

While the specification concludes with claims particularly pointing out and distinctly claiming the invention, it is believed that the present invention will be better understood from the following description.

All percentages, ratios, and levels of ingredients referred to herein are based on the actually total amount of the composition, unless otherwise indicated.

All measurements referred to herein are made at 25°C unless otherwise specified.

All publications, patent applications, and issued patents mentioned herein are hereby incorporated in their entirety by reference. Citation of any reference is not an admission regarding any determination as to its availability as prior art to the claimed invention.

Herein, "comprising" means that other steps and other ingredients which do not affect the end result can be added. This term encompasses the terms "consisting of" and "consisting essentially of."

Herein, "topical application" means to apply or spread a material onto the surface of the skin.

Herein, "skin lightening" refers altering the appearance of the skin to a brighter, lighter, and/or whiter appearance, and improving hyperpigmentation as compared to pre-treatment.

Herein, "cosmetically-acceptable" means that the compositions or components thereof so described are suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, and the like.

Herein, "safe and effective amount," means an amount of a compound or composition sufficient to significantly induce a positive benefit, preferably a positive skin appearance or feel benefit, including independently the benefits disclosed herein, but low enough to avoid serious side effects, *e.g.*, to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

Herein, "mixtures" is meant to include a simple combination of materials and any compounds that may result from their combination.

All ingredients such as actives and other ingredients useful herein may be categorized or described by their cosmetic and/or therapeutic benefit or their

postulated mode of action. However, it is to be understood that the active and other ingredients useful herein can, in some instances, provide more than one cosmetic and/or therapeutic benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit an ingredient to the particularly stated application or applications listed.

The present invention is directed to a composition comprising an ascorbic acid compound, a charged, reflective particulate material, a structuring compound, and a cosmetically-acceptable carrier.

Without being bound by theory, it is believed that a high reduction capability of the ascorbic acid compound provides promotion of cell respiration, enzyme activation and anti-oxidation. It is further believed topical application of the ascorbic acid compound tends to reduce oxidized melanin complex itself and its precursors, as well as inhibit tyrosinase activity in the melanosome. Consequently, it is also believed that compositions containing the ascorbic acid compound can provide skin benefits such as the prevention of melanin production and the reduction of age spots, blotches and/or freckles associated with skin hyperpigmentation.

Increasing the concentration of ascorbic acid in compositions will typically improve the efficacy of the composition. For example, increasing the level of ascorbic acid in a skin lightening composition will result in improved lightening of the skin. Unfortunately, in the past it has been difficult to increase these levels because compositions having such increased levels of ascorbic acid tend to be unstable, particularly uneatable in physical properties, such as product appearance changing to yellow or brown. However, we have discovered that including a structuring compound in a composition can sustain the original physical properties of an ascorbic acid compound and the composition thereof, even when the composition contains relatively high levels of the ascorbic acid compound. Such improvement of stability is particularly effective in an aqueous composition.

A. Ascorbic Acid Compound

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The composition of the present invention includes an ascorbic acid compound. The ascorbic acid compound is selected depending upon its compatibility with the other ingredients. The ascorbic acid compound may be included as a substantially pure material, for example, which may be an extract

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obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources.

The composition of the present invention, preferably contains from about 1.0% to about 10.0% of the ascorbic acid compound, more preferably from about 2.0% to about 5.0%.

Herein, "ascorbic acid compound," means ascorbic acid or derivatives thereof which have the formula (I):

$$V \longrightarrow W$$

$$O \longrightarrow H$$

$$R1$$
(I)

wherein V and W are independently -OH; R¹ is - CH(OH)-CH₂OH; and salts thereof.

Preferably, the ascorbic acid compound useful herein is an ascorbic acid salt or derivative thereof, such as the non-toxic alkali metal, alkaline earth metal and ammonium salts commonly known by those skilled in the art including, but not limited to, the sodium, potassium, lithium, calcium, magnesium, barium, ammonium and protamine salts which are prepared by methods well known in the art.

More preferably, the ascorbic acid salt useful herein is a metal ascorbate having the following formula (II):

wherein R^2 and R^3 are independently selected from hydrogen and linear or branched alkyl of 1 to about 8 carbons; M^1 is a metal; and x is an integer of from 1 to about 3. More preferably, R^2 and R^3 are independently selected from hydrogen and linear or branched alkyl of 1 to about 3 carbons; M^1 is sodium, potassium, magnesium, or calcium.

Examples of other preferred ascorbic acid salts having formula (II) include monovalent metal salts (e.g., sodium ascorbate, potassium ascorbate), divalent

metal salts (e.g., magnesium ascorbate, calcium ascorbate) and trivelent metal salts (e.g., aluminum ascorbate) of ascorbic acid.

Preferably, the ascorbic acid salt useful herein is a water soluble ascorbyl ester having the following formula (III):

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wherein A is sulfate or phosphate; R^4 and R^5 are independently selected from hydrogen and linear or branched alkyl of 1 to about 8 carbons; M^2 is a metal; and y is an integer of 1 to about 3. More preferably, R^4 and R^5 are independently selected from hydrogen and linear or branched alkyl of 1 to about 3 carbons; M^2 is sodium, potassium, magnesium, or calcium.

Exemplary water soluble salt derivatives include, but are not limited to, L-ascorbyl phosphate ester salts such as sodium L-ascorbyl phosphate, potassium L-ascorbyl phosphate, magnesium L-ascorbyl phosphate, calcium L-ascorbyl phosphate, aluminum L-ascorbyl phosphate. L-ascorbyl sulfate ester salts can also be used. Examples are sodium L-ascorbyl sulfate, potassium L-ascorbyl sulfate, magnesium L-ascorbyl sulfate, calcium L-ascorbyl sulfate and aluminum L-ascorbyl sulfate.

B. Charged, Reflective Particulate Material

The compositions of the present invention also essentially comprise from about 0.01% to about 5.0%, preferably from about 0.1% to about 5.0%, more preferably from about 0.5% to about 2.0%, by weight of the composition, of a charged, reflective particulate material ("charged material").

The charged material, preferably comprises a reflective particulate material such as titanium dioxide which is coated with a coating material that confers a net charge that is greater than the zeta potential of the uncoated metallic oxide. Such charged material can be dispersed throughout the carrier.

Without being limited by theory, it is believed that reflective particulate materials, such as titanium dioxide, generally possess relatively high surface activity, creating formulation instabilities. In addition, these reflective particulate materials have a tendency to agglomerate, e.g., clump together, resulting in precipitation of the reflective particulate materials. These problems can be

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solved by coating the reflective particulate material (metallic oxide) with a coating material that confers a net charge that is greater than the zeta potential of the uncoated reflective particulate material. Typically, the coating material confers a zeta potential that is greater than about ±20 mV (e.g., either in the positive or negative direction) at pH from about 4 to about 8.5. Further such coating materials provide reflective particulate materials with steric hindrance, resulting in preventing agglomeration of such charged materials. This provides formulation stability and prevents agglomeration of the reflective particulate materials (metallic oxide). Particulates and their charges are well known to those of ordinary skill in the art, and are well described in R.J Hunter, Zeta Potential in Principles and Application (1981), published by Academic Colloid Science: Press; J.N. Israelachvili, Intermolecular and Surface Forces: With Applications to Colloidal and Biological Systems (1985), published by Academic Press; and Hoogeven, N.G. et al., Colloids and Surfaces, Physiochemical and Engineering Aspects, Vol. 117, p. 77 (1966). All of these publications are incorporated herein by reference in their entirety.

Preferably, the charged materials all have a net cationic charge or a net anionic charge. It is believed that because all of the particles have the same charge, the repulsive forces prevent agglomeration and induce even distribution throughout the hydrophilic phase. As a result, (i) lower concentrations of the reflective particulate material give maximum visible light reflection in a composition, (ii) aesthetic negative impact such as chalky and gritty feel are not created, and (iii) formulation instabilities are decreased. Thus, the use of charged materials provide efficient coverage at relatively low levels of the charged materials.

The charged materials useful in the compositions of the present invention will generally have a refractive index of at least about 2, more preferably at least about 2.5, e.g., from about 2 to about 3. Refractive index can be determined by conventional methods. For example, a method for determining the refractive index which is applicable to the present invention is described in J. A. Dean, Ed., Lange's Handbook of Chemistry, 14th Ed., McGraw Hill, New York, 1992, Section 9, Refractometry, incorporated herein by reference in its entirety.

Preferred charged materials are those having an primary particle size of from about 100 nm to about 300 nm, more preferably from about 100 to about 250 nm in the neat form (i.e., in the essentially pure, powder form prior to

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combination with any carrier). Preferred charged materials have a primary particle size when dispersed in the composition of from about 100 nm to about 100 nm, more preferably from about 100 nm to about 400 nm, even more preferably from about 200 nm to about 300 nm. Primary particle size can be determined using the ASTM Designation E20 - 85 "Standard Practice for Particle Size Analysis of Particulate Substances in the Range of 0.2 to 75 Micrometers by Optical Microscopy", ASTM Volume 14.02, 1993, incorporated herein by reference.

The particles may have a variety of shapes, including spherical, spheroidal, elliptical, lamellar, irregular, needle and rod-like, provided that the desired refractive index is provided. The particulate can be in a variety of physical forms, including rutile, anatase or a combination thereof.

(i) Reflective Particulate Material: The reflective particulate material herein is metallic oxide, preferably comprises particles of inorganic material such as titanium dioxide, zinc oxide, zirconium dioxide, aluminum oxide, and combinations thereof, more preferably titanium dioxide, zinc oxide and combinations thereof (combinations are intended to include particles which comprise one or more of these materials, as well as mixtures of these particulate materials) and most preferably, the particles consist essentially of titanium dioxide. The reflective particulate material may be a composite, e.g., deposited on a core or mixed with other materials such as, but not limited to, silica, silicone resin, mica, and nylon.

Inorganic particulate materials, *e.g.*, titanium dioxide, zinc oxide, zirconium dioxide, or aluminum oxide are commercially available from a number of sources. One example of a suitable particulate material comprises Tronox[™] (titanium dioxide series) and SAT-T CR837 (a rutile Titanium dioxide) available from U. S. Cosmetics, titanium dioxide CR-50 available from Ishihara Sangyo Kaisha, and titanium dioxide JA-1 available from Tayca Corporation.

The compositions may contain other inorganic or organic particulate materials. However, it is preferred that the particulates in the compositions of the invention consist essentially of the particulate material described in this section.

(ii) Coating Material: The reflective particulate materials described hereinbefore are preferably coated with a coating material that confers a net charge that is greater than the zeta potential of the uncoated reflective particulate material. Therefore, any coating material can be used as long as the net charge

(cationic or anionic) conferred to the reflective particulate is greater than the untreated reflective particulate material. However, all of the particulates within a composition are preferably treated with the same net charge, e.g., no mixing of cationic and anionic coating materials, to benefit from the repulsive forces between the reflective particulates. It is understood by one skilled in the art, however, that small amounts of oppositely charged coating materials may be used, as long as, the overall repulsive forces are maintained.

Nonlimiting examples of coating materials that confer a cationic charge include cationic polymers (natural and/or synthetic) and cationic surfactants. Preferred cationic coating materials are selected from the group consisting of chitosan, hydroxypropyl chitosan, quaternium-80, polyquaternium-7, and mixtures thereof.

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Nonlimiting examples of coating materials that confer an anionic charge include anionic polymers (natural and/or synthetic) and anionic surfactants. Preferred anionic coating materials are selected from the group consisting of ammonium polyacrylate, sodium polyacrylate, potassium polyacrylate, ethylene acrylic acid copolymer, hydrolyzed wheat protein polysiloxane copolymer, dimethicone copolyol phosphate, dimethicone copolyol acetate, dimethicone copolyol laurate, dimethicone copolyol stearate, dimethicone copolyol behenate, dimethicone copolyol isostearate, dimethicone copolyol hydroxystearate, phosphate ester, sodium chondroiton sulfate, sodium hyaluronate, ammonium hyaluronate, sodium algenate, ammonium algenate, ammonium laurate, sodium laurate, potassium laurate, ammonium myristate, sodium myristate, potassium myristate, ammonium palmitate, sodium palmitate, potassium palmitate, ammonium stearate, sodium stearate, potassium stearate, ammonium oleate, sodium oleate, potassium oleate, and mixtures thereof. More preferred are anionic coating materials selected from the group consisting of ammonium polyacrylate, sodium polyacrylate, and mixtures thereof.

The charged materials (e.g., treated with the coating material) are available in essentially neat, powdered form, or predispersed in various types of carriers, including but not limited to water, organic hydrophilic diluents such as lower monovalent alcohols (e.g., C₁₋₄) and low molecular weight glycols and polyols, including propylene glycol, polyethylene glycol (e.g., Molecular Weight 200-600 g/mole), polypropylene glycol (e.g., Molecular Weight 425-2025 g/mole), glycerol, butylene glycol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol,

ethanol, isopropanol, sorbitol esters, butanediol, ether propanol, ethoxylated ethers, propoxylated ethers and combinations thereof. Preferably, the charged particulate materials are predispersed in water, glycerin, butylene glycol, propylene glycol, and mixtures thereof. Examples of commercially available charged particulate materials include Kobo BG60DC (a predispersion of chitosan treated titanium dioxide and butylene glycol), Kobo GLW75CAP (a predispersion of ammonium polyacrylate treated titanium dioxide, water, and glycerin), Kobo GLW75CAP-MP (a predispersion of ammonium polyacrylate treated titanium dioxide, water, glycerin, methylparaben, and propylparaben) all available from Kobo Products Inc., located in South Plainfield, NJ.

Structuring Compound

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The composition of the present invention comprises a structuring compound. Herein, "structuring compound" refers to a compound which forms an organized structure, a gel network system, such that the system can exist in hydrophobic or hydrophilic components. It is believed that the structuring compound assists in providing good rheological characteristics to the composition which contribute to the stability and pleasant aesthetic characteristics of the composition. Preferably, the structuring compound is present from about 1.0% to about 10.0%, more preferably from about 2.0% to about 8.0% in the composition.

Preferably, the structuring compound comprises a fatty alcohol and an amphiphilic surfactant. While not wishing to be bound by theory, it is believed that the fatty alcohol, together with the amphiphilic surfactant, is oriented in order to form a lamellar structure, resulting in sustaining oil and water phases. It is also believed such an organized structure, called "fatty alcohol gel network system," contribute to stability of the composition.

The fatty alcohols useful herein are an linear or branched, saturated fatty alcohol, selected from the group consisting of linear or branched, saturated C₁₂-30 fatty alcohols, linear or branched, saturated C₁₂₋₃₀ diols, and mixtures thereof. Preferred fatty alcohols are cetyl alcohol, stearyl alcohol, and mixtures thereof. Preferably, the fatty alcohols useful herein present from about 1.0% to 10.0% in the composition, more preferably from about 1.0% to about 5.0%.

The amphiphilic surfactant useful herein includes surfactants, any of a wide variety of nonionic, cationic, anionic, zwitterionic, amphoteric as well as mixtures of these surfactants. Examples of a broad variety of additional

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surfactants useful herein are described in McCutcheon's Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation, which is incorporated herein by reference in its entirety. Also see U.S. Patent No. 4,800,197, to Kowcz et al., issued January 24, 1989, which is incorporated herein by reference in its entirety, for exemplary surfactants useful herein. Preferably, the amphiphilic surfactants useful herein present from about 1.0% to 10.0% in the composition, more preferably from about 2.0% to about 6.0%.

Preferred nonionic surfactants useful herein are the condensation products of alkylene oxides with both fatty acids and fatty alcohols (e.g., wherein the polyalkylene oxide portion is esterified on one end with a fatty acid and etherified (e.g., connected via an ether linkage) on the other end with a fatty alcohol). These materials have the general formula $R^2CO(X^1)_ZOR^3$ wherein R^2 and R^3 are independently alkyl of from about 10 to about 30 carbons; X^1 is - OCH_2CH_2 derived from, for example ethylene glycol or oxide or - OCH_2CHCH_3 -derived from propylene glycol or oxide; and z is an integer from about 6 to about 100.

Other examples of such alkylene oxide derived nonionic surfactants include ceteth-6, ceteth-10, ceteth-12, ceteareth-6, ceteareth-10, ceteareth-12, ceteareth-20, steareth-20, steareth-10, steareth-12, steareth-20, steareth-21, steareth-100, PEG-6 stearate, PEG-10 stearate, PEG-12 stearate, PEG-100 stearate, PEG-10 glyceryl stearate, PEG-30 glyceryl cocoate, PEG-80 glyceryl cocoate, PEG-80 glyceryl cocoate, PEG-80 glyceryl tallowate, PEG-200 glyceryl tallowate, PEG-8 dilaurate, PEG-10 distearate, glyceryl monostearate, gylceryl distearate, glyceryl monostearate, glyceryl dilaurate and mixtures thereof.

The structuring compound may further contain a co-thickener. Exemplary co-thickeners useful herein are polysaccharides and materials which are primarily derived from natural sources such as gums.

A wide variety of the polysaccharides known in the art may be used. "Polysaccharides" as used herein means an ingredient containing a backbone of repeating sugar (i.e. carbohydrate) units. Nonlimiting examples of such polysaccharides include those selected from the group consisting of cellulose, carboxymethyl hydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethyl ethylcellulose, hydroxypropylcellulose,

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hydroxypropyl methylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof.

Also useful herein are the alkyl substituted celluloses. In these polymers, the hydroxy groups of the cellulose polymer is hydroxyalkylated (preferably hydroxyethylated or hydroxypropylated) to form a hydroxyalkylated cellulose which is then further modified with a C₁₀₋₃₀ straight chain or branched chain alkyl group through an ether linkage. Typically these polymers are ethers of C₁₀₋₃₀ straight or branched chain alcohols with hydroxyalkylcelluloses. Examples of alkyl groups useful herein include those selected from the group consisting of stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e. alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. Preferred among the alkyl hydroxyalkyl cellulose ethers is the material given the CTFA designation hydroxyethylcellulose, which is the ether of cetyl alcohol and hydroxyethylcellulose. This material is sold under the tradename Natrosol® CS Plus from Aqualon Corporation.

Other useful polysaccharides include scleroglucans comprising a linear chain of (less than 3) linked glucose units with a less than 6 linked glucose every three units, a commercially available example of which is Clearogel™ CS11 from Michel Mercier Products Inc. (Mountainside, NJ).

Nonlimiting examples of the gums include materials selected from the group consisting of acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar hydroxypropyltrimonium chloride, hectorite, hyaluroinic acid, hydrated silica, hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate, potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboyxmethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof.

Cosmetically-Acceptable Carrier 30

The composition of the present invention comprises a cosmeticallyacceptable carrier. Herein, "cosmetically-acceptable carrier" means one or more compatible solid or liquid fillers, diluents, extenders and the like, which are cosmetically acceptable as defined herein. The term "compatible" herein means that the components of the compositions of this invention are capable of being

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commingled with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations.

The cosmetically-acceptable carrier useful herein is selected from the group consisting of a hydrophobic component, a hydrophilic liquid carrier, a pH adjuster, water, and mixtures thereof. The type of the carrier utilized in the present invention depends on the type of the product desired and may comprise several types of carriers including, but not limited to, solutions, aerosols, emulsions (including oil-in-water or water-in-oil), gels, solids, and liposomes.

1) Hydrophobic Component

Hydrophobic components useful in the present invention include a lipid, oil, oily or other hydrophobic component. The hydrophobic component is used as an emollient.

A wide variety of suitable hydrophobic components are known and may be used herein and numerous examples can be found in Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972). Nonlimiting examples of suitable hydrophobic components include mineral oil, petrolatum, C_{7-40} straight and branched hydrocarbons, C_{1-30} alcohol esters, glycerides, alkylene glycol esters, propoxylated and ethoxylated derivatives, sugar ester, vegetable oils and hydrogenated vegetable oils, animal fats and oils, and C_{4-20} alkyl ethers of polypropylene glycols, C_{1-20} carboxylic acid esters of polypropylene glycols, and di- C_{8-30} alkyl ethers. Examples of hydrophobic components useful herein are set forth in U.S. Patent 5,306,514, Letton et al., issued April 26, 1994; Merck Index, Tenth Edition, Entry 7048, p. 1033 (1983); and International Cosmetic Ingredient Dictionary, Fifth Edition, vol. 1, p.415-417 (1993).

A fatty acid sugar ester useful herein is C_{1-30} monoester or polyester of sugars and one or more carboxylic acid moieties, preferably a sucrose polyester in which the degree of esterification is 7-8, and in which the fatty acid moieties are C_{18} mono- and/or di-unsaturated and behenic, in a molar ratio of unsaturates:behenic of 1:7 to 3:5, more preferably the octaester of sucrose in which there are about 7 behenic fatty acid moieties and about 1 oleic acid moiety in the molecule, *e.g.*, sucrose ester of cottonseed oil fatty acids.

Preferably, the composition contains from about 2.0% to about 95.0% of the hydrophobic component, more preferably from about 40.0% to about 85.0%.

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The hydrophobic component may include an ingredient derived from animals, plants, or petroleum and which is natural or synthetic (e.g., man-made).

2) Hydrophilic Liquid Carrier

The composition of the present invention may contain a hydrophilic liquid carrier (HLC). Preferred HLC can contain a dermatologically acceptable, non-aqueous hydrophilic diluent. Nonlimiting examples of hydrophilic diluents are polyhydric alcohols such as low molecular weight monovalent alcohols (*i.e.*, C₁₋₆) and low molecular weight glycols and polyols including propylene glycol, butylene glycol, hexylene glycol, dipropylene glycol, polyethylene glycol (*e.g.*, Molecular Weight 200-1000 g/mole), polypropylene glycol (*e.g.*, Molecular Weight 425-2025 g/mole), glycerol, 1,2,4-butanetriol, 1,2,6-hexanetriol, and combinations thereof.

Preferably, the composition contains from about 30% to about 95% of HLC, more preferably from about 40% to about 90%. The HLC includes water and one or more water soluble or dispersible ingredients. The exact amount of water in the formulation will vary with the ranges of the required and optional components chosen.

3) pH Adjuster

The cosmetically-acceptable useful herein may contain a pH adjuster. Herein, "pH adjuster" refers to any component which is employed to increase or decrease the overall pH of the composition to an optimum pH, thereby preventing decomposition of ingredients (particularly the ascorbic acid compound). An optimum pH is subject to the selection of the ascorbic acid compound. For example, when the composition includes magnesium L-ascorbyl phosphate (MAP), the optimum pH is around 7.0 to about 8.0. Suitable pH adjusters herein include acetate, phosphate, citrate, triethanolamine and carbonate. A combination of the foregoing are often employed to adjust to a specific optimal pH for the composition. The total level by weight of total composition of the pH adjuster is from about 0.01% to about 5.0%, preferably, from about 0.5% to about 2.0%.

4) Other Actives

The cosmetically-acceptable useful herein may further contain other actives capable of functioning in different ways to enhance the benefits of the ascorbic acid compound and/or to provide other benefits. Examples of such substances include, but are not limited to, a vitamin B₃ compound, anti-oxidants

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and radical scavengers, anti-inflammatory agents, antimicrobial agents, sunscreens and sunblocks, and chelators. Other actives useful herein include vitamin A (e.g., retinoid which are commercially available from a number of sources, for example, Sigma Chemical Company (St. Louis, MO), and Boerhinger Mannheim (Indianapolis, IN) and described in U.S. Patent 4,677,120, Parish et al., issued Jun. 30, 1987; U.S. Patent 4,885,311, Parish et al., issued Dec. 5, 1989; U.S. Patent 5,049,584, Purcell et al., issued Sep. 17, 1991; U.S. Patent 5,124,356, Purcell et al., issued Jun. 23, 1992; and Reissue Patent 34,075, Purcell et al., issued Sep. 22, 1992); and vitamin K.

(i) Vitamin B₃ Compounds: The vitamin B₃ compound enhances the skin appearance benefits of the present invention, especially in regulating skin condition, including regulating signs of skin aging, more especially wrinkles, lines, and pores. The vitamin B₃ compound preferably present from about 0.01% to about 50%, more preferably from about 0.1% to about 10%, even more preferably from about 0.5% to about 10%, and still more preferably from about 1% to about 5%.

Herein, "vitamin B₃ compound" means a compound having the formula:



wherein R is -CONH₂ (e.g., niacinamide), -COOH (e.g., nicotinic acid) or -CH₂OH (e.g., nicotinyl alcohol); derivatives thereof; and salts of any of the foregoing.

Exemplary derivatives of the foregoing vitamin B₃ compounds include nicotinic acid esters, including non-vasodilating esters of nicotinic acid, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide.

Suitable esters of nicotinic acid include nicotinic acid esters of from 1 to about 22 carbons, preferably 1 to about 16 carbons, more preferably alcohols from about 1 to about 6 carbons. The alcohols are suitably straight-chain or branched chain, cyclic or acyclic, saturated or unsaturated (including aromatic), and substituted or unsubstituted. The esters are preferably non-vasodilating. As used herein, "non-vasodilating" means that the ester does not commonly yield a visible flushing response after application to the skin in the subject compositions (the majority of the general population would not experience a visible flushing

response, although such compounds may cause vasodilation not visible to the naked eye, *i.e.*, the ester is non-rubifacient). Non-vasodilating esters of nicotinic acid include tocopherol nicotinate and inositol hexanicotinate; tocopherol nicotinate is preferred.

Other derivatives of the vitamin B₃ compound are derivatives of niacinamide resulting from substitution of one or more of the amide group hydrogens. Nonlimiting examples of derivatives of niacinamide useful herein include nicotinyl amino acids, derived, for example, from the reaction of an activated nicotinic acid compound (e.g., nicotinic acid azide or nicotinyl chloride) with an amino acid, and nicotinyl alcohol esters of organic carboxylic acids (e.g., 1 to about 18 carbons). Specific examples of such derivatives include nicotinuric acid (C₈H₈N₂O₃) and nicotinyl hydroxamic acid (C₆H₆N₂O₂), which have the following chemical structures:

nicotinuric acid:

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nicotinyl hydroxamic acid:

Exemplary nicotinyl alcohol esters include nicotinyl alcohol esters of the carboxylic acids salicylic acid, acetic acid, glycolic acid, palmitic acid and the like. Other non-limiting examples of vitamin B₃ compounds useful herein are 2-chloronicotinamide, 6-aminonicotinamide, 6-methylnicotinamide, n-methylnicotinamide, n,n-diethylnicotinamide, n-(hydroxymethyl)-nicotinamide, quinolinic acid imide, nicotinanilide, n-benzylnicotinamide, n-ethylnicotinamide, nifenazone, nicotinaldehyde, isonicotinic acid, methyl isonicotinic acid, thionicotinamide, nialamide, 1-(3-pyridylmethyl) urea, 2-mercaptonicotinic acid, nicomol, and niaprazine.

Nonlimiting examples of the above vitamin B₃ compounds are well known in the art and are commercially available from a number of sources, e.g., the

Sigma Chemical Company (St. Louis, MO); ICN Biomedicals, Inc. (Irvin, CA) and Aldrich Chemical Company (Milwaukee, WI).

One or more vitamin B₃ compounds may be used herein. Preferred vitamin B₃ compounds are niacinamide and tocopherol nicotinate. Niacinamide is more preferred.

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When used, salts, derivatives, and salt derivatives of niacinamide are preferably those having substantially the same efficacy as niacinamide in the methods of regulating skin condition described herein.

Salts of the vitamin B₃ compound are also useful herein. Nonlimiting examples of salts of the vitamin B₃ compound useful herein include organic or inorganic salts, such as inorganic salts with anionic inorganic species (*e.g.*, chloride, bromide, iodide, carbonate, preferably chloride), and organic carboxylic acid salts (including mono-, di- and tri- C₁₋₁₈ carboxylic acid salts, *e.g.*, acetate, salicylate, glycolate, lactate, malate, citrate, preferably monocarboxylic acid salts such as acetate). These and other salts of the vitamin B₃ compound can be readily prepared by the skilled artisan, for example, as described by W. Wenner, "The Reaction of L-Ascorbic and D-losascorbic Acid with Nicotinic Acid and Its Amide", J. Organic Chemistry, Vol. 14, 22-26 (1949). Wenner describes the synthesis of the ascorbic acid salt of niacinamide.

In a preferred embodiment, the ring nitrogen of the vitamin B₃ compound is substantially chemically free (e.g., unbound and/or unhindered), or after delivery to the skin becomes substantially chemically free ("chemically free" is hereinafter alternatively referred to as "uncomplexed"). More preferably, the vitamin B₃ compound is essentially uncomplexed. Therefore, if the composition contains the vitamin B₃ compound in a salt or otherwise complexed form, such complex is preferably substantially reversible, more preferably essentially reversible, upon delivery of the composition to the skin. For example, such complex should be substantially reversible at a pH of from about 5.0 to about 6.0. Such reversibility can be readily determined by one having ordinary skill in the art.

More preferably the vitamin B₃ compound is substantially uncomplexed in the composition prior to delivery to the skin. Exemplary approaches to minimizing or preventing the formation of undesirable complexes include omission of materials which form substantially irreversible or other complexes with the vitamin B₃ compound, pH adjustment, ionic strength adjustment, the use

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of surfactants, and formulating wherein the vitamin B₃ compound and materials which complex therewith are in different phases. Such approaches are well within the level of ordinary skill in the art.

Thus, in a preferred embodiment, the vitamin B₃ compound contains a limited amount of the salt form and is more preferably substantially free of salts of a vitamin B₃ compound. Preferably the vitamin B₃ compound contains less than about 50% of such salt, and is more preferably essentially free of the salt form. The vitamin B₃ compound in the compositions hereof having a pH of from about 4 to about 7 typically contain less than about 50% of the salt.

The vitamin B₃ compound may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources. The vitamin B₃ compound is preferably substantially pure, more preferably essentially pure.

(ii) Anti-Oxidants and Radical Scavengers: Anti-oxidants and radical scavengers are especially useful for providing protection against UV radiation which can cause increased scaling or texture changes in the stratum corneum and against other environmental agents which can cause skin damage.

Anti-oxidants and radical scavengers such as tocopherol (vitamin E), tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename Trolox®), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, amines (*i.e.*, N,N-diethylhydroxylamine, aminoguanidine), sulfhydryl compounds (*i.e.*, glutathione), dihydroxy fumaric acid and its salts, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and rosemary extracts may be used. Preferred anti-oxidants/radical scavengers are selected from tocopherol sorbate and other esters of tocopherol, more preferably tocopherol sorbate. For example, the use of tocopherol sorbate in topical compositions and applicable to the present invention is described in U.S. Patent 4,847,071, Bissett et al, issued July 11, 1989.

(iii) Anti-Inflammatory Agents Anti-inflammatory agents enhance the skin appearance benefits, by for example, contribution of uniformity and acceptable skin tone and/or color.

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Preferably, the anti-inflammatory agent includes a steroidal anti-inflammatory agent and an non-steroidal anti-inflammatory agent. Preferred steroidal anti-inflammatory for use is hydrocortisone.

The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974), each incorporated herein by reference.

So-called "natural" anti-inflammatory agents are also useful. Such agents may suitably be obtained as an extract by suitable physical and/or chemical isolation from natural sources (*i.e.*, plants, fungi, by-products of microorganisms). For example, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly Rubia Cordifolia), and Guggal (extracted from plants in the genus Commiphora, particularly Commiphora Mukul), kola extract, chamomile, and sea whip extract, may be used.

Additional anti-inflammatory agents useful herein include compounds of the licorice (the plant genus/species Glycyrrhiza glabra) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof (e.g., salts and esters). Suitable salts of the foregoing compounds include metal and ammonium salts. Suitable esters include C_{2-24} saturated or unsaturated esters of the acids, preferably C_{10-24} , more preferably C_{16-24} .

- (iv) Antimicrobial Agent: As used, "antimicrobial agents" means a compound capable of destroying microbes, preventing the development of microbes or preventing the pathogenic action of microbes. Antimicrobal agents are useful, for example, in controlling acne. Preferred antimicrobial agents useful in the present invention are benzoyl peroxide, erythromycin, tetracycline, clindamycin, azelaic acid, sulfur resorcinol phenoxyethanol, and IrgasanTM DP 300 (Ciba Geigy Corp., U.S.A.). A safe and effective amount of an antimicrobial agent may be added to compositions of the present invention, preferably from about 0.001% to about 5%, still more preferably from about 0.05% to about 2%.
- (v) Sunscreens and Sunblocks: Sunscreens and sunblocks generally prevent excessive scaling and texture changes of the stratum corneum by

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exposure of ultraviolet light and may be added to the composition of the present invention. Suitable sunscreens and sunblocks may be organic or inorganic.

A wide variety of conventional sunscreens and sunblocks are suitable for use herein. See, U.S. Patent 5,087,445, Haffey et al, issued February 11, 1992; U.S. Patent 5,073,372, Turner et al, issued December 17, 1991; U.S. Patent 5,073,371, Turner et al., issued December 17, 1991; and Segarin, et al. at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology (1972). which discloses numerous suitable sunscreens and sunblocks. Preferred among those sunscreens and sunblocks which are useful in the compositions are those selected from 2-ethylhexyl-p-methoxycinnamate (commercially available as PARSOL MCX), butylmethoxydibenzoyl-methane, 2-hydroxy-4-methoxybenzophenone, 2-phenylbenzimidazole-5-sulfonic acid, octyldimethyl-p-aminobenzoic acid, octocrylene, 2-ethylhexyl N,N-dimethyl-p-aminobenzoate, p-aminobenzoic acid. 2-phenylbenzimidazole-5-sulfonic acid. octocrylene, oxybenzone. homomenthyl salicylate, octyl salicylate, 4,4'-methoxy-t-butyldibenzoylmethane, 4-isopropyl dibenzoylmethane, 3-benzylidene camphor, 3-(4-methylbenzylidene) camphor, titanium dioxide, zinc oxide, silica, iron oxide, Eusolex™ 6300, Octocrylene, Parsol 1789, and mixtures thereof.

Also particularly useful in the compositions are sunscreens and sunblocks such as those disclosed in U.S. Patent 4,937,370, Sabatelli, issued June 26, 1990, and U.S. Patent 4,999,186, Sabatelli, issued March 12, 1991. The sunscreens and sunblocks disclosed therein have, in a single molecular, two distinct chromophore moieties which exhibit different ultraviolet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range. These sunscreens and sunblocks provide higher efficacy, broader UV absorption, lower skin penetration and longer lasting efficacy relative to conventional sunscreens and sunblocks.

Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF). SPF is a commonly used measure of photoprotection of a sunscreen against erythema. See Federal Register, Vol. 43, No. 166, pp. 38206-38269, August 25, 1978.

A sunscreen or sunblock herein may also be added to improve the skin. particularly to enhance their resistance to being washed off by water, or rubbed off. Preferred sunscreens and sunblocks which will provide this benefit are a

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copolymer of ethylene and acrylic acid. Compositions comprising this copolymer are disclosed in U.S. Patent 4,663,157, Brock, issued May 5, 1987.

(vi) Chelators: As used herein, "chelator" refers to a compound that reacts for removing a metal ion from a system by forming a complex so that the metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelator is especially useful for providing protection against UV radiation which can contribute to excessive scaling or skin texture changes and against other environmental agents which can cause skin damage.

Exemplary chelators that are useful herein are disclosed in U.S. Patent 5,487,884, Bissett et al, issued January 30, 1996; PCT application 91/16035 and 91/16034, Bush et al, published October 31, 1995. Preferred chelators are furildioxime and derivatives thereof.

4) Other components

In addition to the above described components, the composition of the present invention may further include preservatives and preservative enhancers such as water-soluble or solubilizable preservatives including Germall 115, methyl, ethyl, propyl and butyl esters of hydroxybenzoic acid, benzyl alcohol, EDTA, Bronopol (2-bromo-2-nitropropane-1,3-diol) and phenoxypropanol; other skin lightening/evenness agents including kojic acid and arbutin; WO95/23780, Kvalnes et al, published September 8, 1995; skin-conditioning agents; skinpenetration enhancing agents; skin protectants; skin soothing agents; skin healing agents; ultraviolet light absorbers or scattering agents; sequestrants; anti-acne agents; anti-androgens; depilation agents; keratolytic agents/ desquamation agents/ exfoliants such as salicylic acid; panthenol moisturizer such as D-panthenol; soluble or colloidally-soluble moisturizing agents such as hyaluronic acid and starch-grafted sodium polyacrylates such as Sanwet™ IM-1000, IM-1500 and IM-2500 available from Celanese Superabsorbent Materials, Portsmith, VA, USA and described in US Patent 4,076,663; proteins and polypeptides and derivatives thereof; organic hydroxy acids; drug astringents; external analgesics; film formers; absorbents including oil absorbents such as clays and polymeric absorbents; abrasives; anticaking agents; antifoaming agents; binders; biological additives; bulking agents; coloring agents; perfumes, essential oils, and solubilizers thereof; natural extracts; compounds which stimulate collagen production.

E. Method for Making Composition

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The compositions of the present invention are generally prepared by any method conventionally used for providing skin care compositions, particularly for skin lotions, that are known in the art. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, and the like. Typical methods are described in, for example are described in Harry's Cosmeticology, 7th Ed., Harry & Wilkinson (Hill Publishers, London 1982).

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention. Where applicable, ingredients are identified by chemical or CTFA name, or otherwise defined below.

The compositions shown below can be prepared by any conventional method known in the art. Suitable methods and formulations are as follows:

(unit %)

		1000	101
Chemical Name	A	В	C
Magnesium Ascorbyl Phosphate	4.000	3.000	-
Sodium Ascorbyl Phosphate	-	-	2.000
KOBO GLW75CAP-MP1	0.670	1.330	2.000
Stearyl Alcohol	•	1.500	-
Cetyl Alcohol	-	-	1.500
Xanthan gum	0.200	0.020	0.500
Fatty acid ester of sugar	•	1.000	0.500
Glycerol	5.000	9.000	7.000
Glyceryl monostearate		3.000	3.000
PEG 100 Stearate	0.300		-
Ceteareth-10		0.400	0.200
Steareth-21	ı	0.200	0.300
Isononyl Isononanoate	6.000	5.000	3.000
Sodium Citrate	1.000	1.000	1.000
Water	Up to	100%	

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The compositions above described are suitably made as follows:

- (1) Dissolve water soluble contents except for an ascorbic acid compound and sodium citrate, and heat the solution up to about 75 °C;
- 5 (2) Mix a separate water solution of a ascorbic acid compound and sodium citrate and cool the mixture to below about 40° C,
 - (3 Mix (1) and (2) and keep the temperature at about 75 °C;
 - (4) Heat a mixture of the structuring compounds and the oil components to about 80 °C;
- 10 (5) Add the mixture (4) into the water phase (3) followed by high pressure homogenizing; and
 - (6) Add KOBO GLW75CAP-MP and glycerin to the mixture (5) at about 30°C.

The embodiments disclosed and represented by the previous examples have many advantages. For example, the composition herein contains increased levels of ascorbic acid compound for skin lightening, while exhibiting improved product aesthetic such as product appearance unchanging to yellow or brown, even if maintained in storage for extended periods of time.

It is understood that the foregoing detailed description of examples and embodiments of the present invention are given merely by way of illustration, and that numerous modifications and variations may become apparent to those skilled in the art without departing from the spirit and scope of the invention; and such apparent modifications and variations are to be included in the scope of the appended claims.

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What is claimed is:

- 1. A composition comprising:
 - (a) an ascorbic acid compound;
 - (b) a charged, reflective particulate material;
 - (c) a structuring compound; and
 - (d) a cosmetically-acceptable carrier.
- 2. The composition of Claim 1, wherein the structuring compound comprises a fatty alcohol and an amphiphilic surfactant.
- 3. The composition of Claim 2, wherein the cosmetically-acceptable carrier is selected from the group consisting of a hydrophobic component, a hydrophilic liquid carrier, a pH adjuster, and mixtures thereof.
- 4. The composition of Claim 2, wherein the cosmetically-acceptable carrier further comprises at least one other active selected from the group consisting of vitamin B₃ compounds, anti-oxidants and radical scavengers, anti-inflammatory agents, antimicrobial agents, sunscreens and sunblocks, and chelators.
- 5. The composition of Claim 4, wherein the structuring compound further comprises a co-thickener selected from the group consisting of gums and polysaccharides.
- 6. A composition comprising:
 - (a) from about 1.0% to about 10.0% of an ascorbic acid compound:
 - (b) from about 0.01% to about 5.0% of a charged, reflective particulate material;
 - (c) from about 1.0% to about 10.0% of a structuring compound; and
 - (d) from about 30.0% to about 95.0% of a cosmetically-acceptable carrier.

- 7. The composition of Claim 6, wherein the structuring compound comprises from about 1.0% to 10.0% of a fatty alcohol and from about 1.0% to about 10.0% of an amphiphilic surfactant
 - 8. The composition of Claim 7, wherein the cosmetically-acceptable carrier comprises from about 2.0% to about 95.0% of a hydrophobic component, from about 30.0% to about 95.0% of a hydrophilic liquid carrier, and from about 0.01 to about 5.0% of a pH adjuster.

.RNATIONAL SEARCH REPORT

International Application No PCT/US 98/24257

CLASSIFICATION OF SUBJECT MATTER PC 6 A61K7/48 IPC 6 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Category Relevant to claim No. X WO 98 34591 A (BISSETT DONALD LYNN ;DATE 1-8 ROBERT FRANCIS (US); KRAMER GREGORY JOSE) 13 August 1998 (1998-08-13) page 6, paragraph 2 - page 18, paragraph page 23, paragraph 2 - page 27, paragraph page 28, paragraph 2 - page 30, paragraph page 32, paragraph 3 page 33, paragraph 5 - page 34, paragraph example 1 -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the last which is not considered to be of particular relevance invention *E* earlier document but published on or after the international "X" document of particular relevance; the claimed inventio cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but "A" document member of the same patent family later than the priority date claimed Date of making of the international search report Date of the actual completion of the international search 2 4. 08. 99 6 July 1999 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24257

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